

Heavy particle irradiation, neurochemistry and behavior: thresholds, dose–response curves and recovery of function

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Abstract

Exposure to heavy particles can affect the functioning of the central nervous system (CNS), particularly the dopaminergic system. In turn, the radiation-induced disruption of dopaminergic function affects a variety of behaviors that are dependent upon the integrity of this system, including motor behavior (upper body strength), amphetamine (dopamine)-mediated taste aversion learning, and operant conditioning (fixed-ratio bar pressing). Although the relationships between heavy particle irradiation and the effects of exposure depend, to some extent, upon the specific behavioral or neurochemical endpoint under consideration, a review of the available research leads to the hypothesis that the endpoints mediated by the CNS have certain characteristics in common. These include: (1) a threshold, below which there is no apparent effect; (2) the lack of a dose–response relationship, or an extremely steep dose–response curve, depending on the particular endpoint; and (3) the absence of recovery of function, such that the heavy particle-induced behavioral and neural changes are present when tested up to one year following exposure. The current report reviews the data relevant to the degree to which these characteristics are common to neurochemical and behavioral endpoints that are mediated by the effects of exposure to heavy particles on CNS activity.

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1. Introduction

The effects of exposure to ionizing radiation can be categorized in a number of different ways. One way involves making a distinction between stochastic and deterministic effects (Todd, 1989; National Academy of Sciences Report, 1996). Stochastic effects are considered to be those, such as carcinogenesis and genetic mutations, for which there is no threshold and for which increasing dose causes increases in the frequency, but not severity of the effect. As dose increases, there is an increase in the probability of observing the effect. In addition, because stochastic effects occur in mitotic cells,

there is the possibility of repair of radiation-induced damage (e.g., Goodwin et al., 1989). Deterministic effects are those for which there is a threshold dose, such as nausea, above which both the severity and the frequency of the effect increase with increasing dose.

An alternate approach is to categorize the effects of exposure to ionizing radiation on behavioral endpoints in terms of whether they are dependent upon the effects of irradiation on peripheral systems or upon the central nervous system (CNS). Effects mediated by the peripheral systems, which include emesis and radiation-induced taste aversion (CTA) learning, are observed following exposure to all types of radiation, including, electrons, neutrons and protons, as well as heavy particles (Rabin et al., 1989, 1991, 1992).

Endpoints which are typically mediated by the effects of the irradiation on the CNS include changes in neurochemical functioning, particularly of the dopaminergic system, and in behaviors that are dependent upon

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the integrity of that system (Joseph et al., 1992, 1993, 1998, 2000). These behaviors include motor behavior (upper body strength) (Joseph et al., 1992), amphetamine (dopamine)-induced CTA learning (Rabin et al., 1998, 2000), spatial learning and memory (Shukitt-Hale et al., 2000, 2003), and operant conditioning (fixed-ratio bar pressing) (Rabin et al., 2002). These behavioral and neurochemical changes are observed only following exposure to heavy particles and not following exposure to other types of radiation, including gamma rays or neutrons (Rabin et al., 1998, 2000).

The effects of exposure to heavy particles on neurochemical and behavioral endpoints can be characterized along three dimensions: (1) threshold – is there a dose below which there is no apparent effect; (2) dose–response relationships – does increasing dose produce corresponding increases in the specific endpoint; and (3) recovery of function – is there a recovery from the deleterious effects of irradiation as a function of time. The purpose of the present paper is to characterize centrally-mediated endpoints along these dimensions by reviewing relevant, albeit somewhat limited, data that we have obtained to date. In addition, the review will allow a consideration of whether the centrally mediated effects can be categorized as stochastic or deterministic effects of exposure to heavy particles.

The specific endpoints that will be considered in this review are:

1. Potassium-stimulated neurochemical release.
2. Motor behavior: specifically upper body strength, measured by placing the forepaws of a rat on a wire and determining the amount of time that the rat can maintain its grip on the wire.
3. Dopamine-mediated CTA, produced by pairing a normally preferred 10% sucrose solution with an injection of amphetamine (3 mg/kg, ip) such that the rat will avoid ingestion of that solution at a subsequent presentation.
4. Operant responding, using an ascending fixed-ratio reinforcement schedule of bar pressing for food reinforcement from FR-1 (every lever press is rewarded) to FR-35 (35 presses required to obtain a single food pellet).

2. Threshold

A comparison of the threshold for various endpoints is summarized in Table 1. The threshold varies as function of particle LET and as a function of the specific endpoint under consideration.

Although the apparent threshold for DA release following exposure to 600 MeV/n and 1 GeV/n ^{56}Fe particles are identical, it should be noted that 0.10 Gy produced a 40% reduction in peak DA release following exposure to 600 MeV/n ^{56}Fe particles compared to a 30% decrease following exposure to the 1 GeV/n particles. While one cannot conclude with absolute certainty that the values presented in the above table do represent the absolute threshold, it may be noted that exposing rats to 0.20 Gy of 522 MeV/n ^{20}Ne particles had no effect on potassium-stimulated DA release, whereas a dose of 0.50 Gy had a maximal effect.

In terms of thresholds for behavioral deficits, exposing rats to 0.50 Gy of 1 GeV/n ^{56}Fe particles did not affect the acquisition of a dopamine-mediated CTA, whereas 0.80 Gy did disrupt CTA learning (Rabin et al., 1998, 2000). Similarly, exposing rats to 1.00 or 1.50 Gy did not disrupt operant responding at the higher fixed-ratio schedules 3 months following exposure. However, the rats that had been exposed to 2.00 Gy failed to increase their responding at the higher fixed ratios (> FR-25) (Rabin et al., 2002).

These observations are consistent with the hypothesis of a threshold, below which the effects on these neurochemical and behavioral endpoints are not observed. If this were not the case, one would have expected to observe some change in these endpoints as the dose increased rather than the absolute change that was obtained. For example, exposing rats to 1.5 Gy might have affected operant responding at a ratio of FR-35 rather than the FR-25 that was observed with the rats exposed to 2.00 Gy of ^{56}Fe (1 GeV/n) particles. Further support for this interpretation is provided by the observation (see below) that once a response was obtained, the response was, for the most part maximal.

Table 1
Thresholds for selected neurochemical and behavioral endpoints

	^{56}Fe (600 MeV/n LET, 189 keV/ μm) (Gy)	^{56}Fe (1 GeV/n LET, 151 keV/ μm) (Gy)	^{20}Ne (522 MeV/n LET, 28 keV/ μm) (Gy)
DA release	0.10 ^a	0.10 ^b	0.50 ^b
Motor	0.10 ^a	0.10 ^b	1.00 ^b
Amphetamine CTA	0.10 ^c	0.80 ^c	–
Operant responding	–	2.00 ^d	–

^a Joseph et al. (1992).

^b Joseph (unpublished).

^c Rabin et al. (1998, 2000).

^d Rabin et al. (2003).

3. Dose–response relationships

To the extent that there are dose–response relationships, the dose–response curves of heavy particle-induced changes in neurochemical function and behavior are extremely steep. Three days following exposure to 600 MeV ^{56}Fe particles, for example, there is a significant decrease in potassium-enhanced striatal DA release as the dose is increased from 0.10 to 0.50 Gy (Joseph et al., 1992). There is no further change in DA release as the dose is increased to 5.00 Gy. In contrast, there is no change in striatal DA release following exposure to 522 MeV/n ^{20}Ne as the dose is increased from the threshold dose of 0.50–1.00 Gy (Joseph, unpublished).

The effects of exposure to heavy particles on behavioral endpoints are similar to that observed using neurochemical endpoints. Upper body strength showed a significant decrease as the dose of 600 MeV/n ^{56}Fe particles was increased from 0.25 to 0.50 Gy. As the dose is further increased to 5.00 Gy, there is no further change in upper body strength (Joseph et al., 1992). The data are less clear following exposure to 1 GeV/n ^{56}Fe particles (Joseph et al., unpublished) because there is an increase in time on the wire as the dose is increased from 0.10 to 0.50 Gy, although the ability of these rats to maintain their grip on the wire is still less than that of the control rats. At a dose of 2.0 Gy, there is a decrease in the amount of time on the wire to a level equal to that observed with the 0.10 Gy dose. The data do not presently allow for a determination of the reasons for the apparent increase in upper body strength at the 0.50 Gy dose.

The data are more linear with respect to the effects of exposure to ^{56}Fe particles on the dopamine (amphetamine)-mediated CTA (Rabin et al., 1998, 2000). For exposure to either 600 MeV/n or 1 GeV/n ^{56}Fe particles, there is no change in the intensity of the amphetamine-induced CTA as the dose is increased from threshold (0.10–1.00 Gy for 600 MeV/n ^{56}Fe particles; 0.80–1.50 Gy for 1 GeV particles). However, as the dose of the 1 GeV/n ^{56}Fe particles is further increased to 2.00 Gy, there is a general reduction in sucrose intake and an increase in the intensity of the CTA produced by injection of both amphetamine and lithium chloride. This change in intake and CTA learning may reflect the general debilitation that accompanies higher doses of irradiation.

4. Recovery of function

The concept of “recovery of function” refers to a return to normal functioning as the time passes following the occurrence of injury to the CNS. In general, there is no recovery of function in adult organisms following bilateral destruction of specific parts of the brain. The results we have obtained following exposure to non-lethal levels of heavy particles is consistent with the

observation of general lack of recovery of function following bilateral damage to neural tissue: there is no apparent recovery of those functions that depend upon the integrity of the dopaminergic system. The reduction in potassium-enhanced striatal DA release observed 12 h following exposure to 0.50 or 1.00 Gy of 600 MeV/n ^{56}Fe particles is still observed 180 days following irradiation (Joseph et al., 1992). The reduction in upper body strength that is correlated with dopaminergic function shows a similar pattern between 12 h and 14 days following irradiation. Whether the reduction in upper body strength is still present 180 following irradiation could not be determined because the non-irradiated rats had gained enough weight to make their ability to maintain their grip on the wire problematical, at best.

For other types of behavior, the relationship between the specific endpoint and the passage of time following irradiation is more complicated. However, the evidence does not appear to support a return to normal function. Rather, what seems to be happening is that there is an interaction between the exposure to heavy particles and the increasing age of the subject. Three days following exposure to 1.00 Gy of 1 GeV/n ^{56}Fe particles, there is a significant decrease in the intensity of the taste aversion produced by injection of amphetamine (Rabin et al., 1998, 2000). When naive rats are tested 112 days following exposure, there is enhanced CTA, possibly due to an up-regulation of the remaining DA receptors; and when they are tested 154 days following exposure, there is no further change in the intensity of the amphetamine-induced CTA observed in the irradiated subjects. However, there is a decrease in the sucrose preference of both the non-irradiated and irradiated subjects due to their increased age.

A clearer interaction with aging is seen with the ability of rats to respond on an ascending fixed-ratio bar pressing task in which the rat has to make an increasing number of presses for a single food pellet (Rabin et al., 2002). When tested 3 months following exposure to 1 GeV/n ^{56}Fe particles, there was no differences in performance between the non-irradiated control rats and the rats exposed to 1.00 or 1.50 Gy. At this time, only the rats exposed to 2.00 Gy showed a significant deficit in performance at the higher ratios (FR-25 to FR-35). When these rats were tested 11 months following exposure, there were no significant differences in performance between any of the three irradiated groups of rats (1.00, 1.50 or 2.00 Gy). All three of these groups showed poorer performance at the higher ratios than did the control rats.

5. Conclusions

Although there remain significant gaps in our ability to characterize the deficits in CNS-mediated endpoints

produced by exposure to heavy particles, the data that is available suggests the following conclusions. First, the neurochemical and behavioral deficits observed following exposure to heavy particles have an apparent threshold below which there are no effects on these endpoints. The absolute threshold varies as a function of both particle LET and endpoint. In general, as particle LET increases, the threshold decreases. The threshold for obtaining deficits in motor performance (upper body strength) is generally lower than that for CTA acquisition, which, in turn, is lower than that for operant responding. These data suggest that the more complex cognitive tasks, such as operant responding, require a greater dose of ^{56}Fe particles to disrupt performance than the more simple motor performance task. Although the presently available data do not provide an explanation for this finding, it is possible that the disruption of cognitive performance requires the loss of a significant proportion of striatal and accumbens dopaminergic neurons (Salamone, 1992), in much the same way as the development of Parkinson's disease.

Second, for many endpoints, e.g. upper body strength or CTA learning, there does not appear to be a dose–response curve. The deficit appears to be maximal when it first appears and increasing the dose does not produce corresponding decreases in performance. Where there does appear to be a dose–response relationship, it appears to be extremely steep, as in the case of striatal DA release following exposure to 600 MeV/n ^{56}Fe particles. Under some conditions, there may be an upper dose limit to the specific deficit produced by exposure. As the dose continues to increase, it causes a general debilitation which disrupts the specific effects of exposure on a range of behavioral endpoints.

Third, within the parameters tested there is no evidence of recovery of function. In and of itself, this observation is not surprising in as much as neurons are post-mitotic. The changes in behavioral endpoints observed as a function of time since exposure to heavy particles may result from the changes in these endpoints (e.g., operant conditioning) that occur as function of the increasing age of the subject. Alternatively, it may be that long-term dopamine loss produced by both exposure to ^{56}Fe particles and age affects the ability of the organism to respond appropriately.

Finally, it is not possible to categorize the neurochemical and cognitive/behavioral effects of exposure to heavy particles as either stochastic or deterministic. While these endpoints have a threshold, which is a characteristic of deterministic effects of irradiation, they lack the second characteristic which is that there is a relationship between the dose of radiation and the intensity of the endpoint. As such, the distinction between the effects of exposure to heavy particles on peripherally- or centrally-mediated endpoints seems to be the most consistent with currently available data.

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